PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

THIOBENCARB

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Agency Secretary
California Environmental Protection Agency
Winston H. Hickox

Director
Office of Environmental Health Hazard Assessment
Joan E. Denton, Ph.D.

Public Health Goal for
THIOBENCARB
In Drinking Water

Prepared by

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Pesticide and Environmental Toxicology Section
Anna M. Fan, Ph.D., Chief

Deputy Director for Scientific Affairs
George V. Alexeeff, Ph.D.

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LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT	REPORT PREPARATION	SUPPORT
Project Director Anna Fan, Ph.D.	***Author*** Jolanta Bankowska, Ph.D.	***Administrative Support*** Edna Hernandez Coordinator Pat Aguilar Jocelyn Tan Genevieve Vivar
Public Workshop Yi Wang, Ph.D.	***Primary Reviewer*** Robert Blaisdell, Ph.D.	
External Review David Ting, Ph.D.	***Final Reviewers*** Anna Fan, Ph.D. George Alexeeff, Ph.D. Robert Howd, Ph.D.	***Library Support*** Charleen Kubota, M.L.S. Valerie Walter
Revisions/Responses Robert Howd, Ph.D.	***Education and Outreach/Summary Documents*** Hanafi Russell	***Web site Posting*** Edna Hernandez Laurie Monserrat

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or

MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR THIOBENCARB IN DRINKING WATER

SUMMARY

A public health goal (PHG) of 70 µg/L (70 ppb) is developed for thiobencarb {S- [(4-chlorophenyl)-methyl] diethylcarbamothioate} in drinking water. The value comprises the parent compound (thiobencarb), its chlorobenzyl and chlorophenyl moiety-containing degradation products and oxidation products such as thiobencarb sulfoxide, thiobencarb sulfone, and 4-chlorobenzosulfonic acid. The oxidation products may be produced during water treatment procedures. The PHG is based on noncarcinogenic effects such as decreased body weight gain, food consumption, and food efficiency identified in a chronic toxicity/carcinogenicity feeding study in rats (Ashby, 1984). The no-observed-adverse-effect-level (NOAEL) identified from this study is 1 mg/kg-day and the lowest-observed-adverse-effect-level (LOAEL) is 5 mg/kg-day. The PHG was calculated assuming an adult body weight of 70 kg, a water consumption rate of 2 L/day, a 20 percent exposure to thiobencarb from drinking water and using an uncertainty factor of 100 to account for inter- and intra-species extrapolation from a chronic animal study to humans.

The existing California maximum contaminant level (MCL) for thiobencarb in drinking water is 70 ppb. No U.S. Environmental Protection Agency (U.S. EPA) MCL has been established.

INTRODUCTION

The purpose of this document is to develop a PHG for thiobencarb. Thiobencarb is not currently regulated under the Safe Drinking Water Act (SDWA). Therefore, no federal MCL has been established by the U.S. EPA. The California MCL for thiobencarb is 70 ppb (DHS, 1999). California also has established a secondary maximum contaminant level (SMCL) of 1 ppb for thiobencarb to avoid the bitter taste (DHS, 1999). Both standards are part of California's drinking water regulations.

Thiobencarb was ranked by the U.S. EPA reference dose (RfD)/Peer Review Committee as a Group D chemical, that is, not classifiable as to human carcinogenicity (February 8, 1996) (U.S. EPA RED, 1997).

In this document, we evaluate data on the toxicity of thiobencarb, primarily by the oral route, and include information available since the previous assessment (DHS, 1987). Our review of the available data includes current online information via Medline, Toxline, Registry of Toxic Effects of Chemical Substances (RTECS), Integrated Risk Information System (IRIS), and Hazardous Substances Data Bank (HSDB) (1999a,b). In our previous (DHS, 1987) as well as current PHG development for thiobencarb, we did not review the original, proprietary studies. We used secondary sources such as detailed reviews by the Department of Pesticide Regulation (DPR) and U.S. EPA.

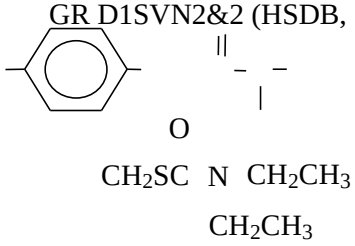
To determine a public health-protective level of thiobencarb in drinking water, relevant articles were identified, reviewed and evaluated. New data on thiobencarb, especially those useful for risk assessment, are very limited. We did not identify any new studies that would be more appropriate for the quantitative risk assessment than the ones already previously reviewed (DHS, 1987).

CHEMICAL PROFILE

Chemical Identity

Thiobencarb is a member of the thiocarbamate group. It consists of a diethylthiocarbamate attached to a chlorobenzyl moiety. The chemical formula, structure, synonyms, and identification numbers are listed in Table 1.

Table 1. Chemical Identity of Thiobencarb.

Property	Information
Chemical name	S- [(4-chlorophenyl) methyl] diethylcarbamothioate
Synonyms	S- (4-Chlorobenzyl) N, N-diethylthiocarbamate S- (p-Chlorobenzyl) diethylthiocarbamate S-4-Chlorobenzyl diethyl (thiocarbamate) Diethyl-carbamothioic acid S- [(4-chlorophenyl) methyl) ester] Alpha-toluenethiol, p-chloro-, diethylcarbamate
Common names	Thiobencarb (ISO-E, ANSI, BSI, WSSA); thiobencarbe (ISO-F); benthiocarb (JMAF)
Trade and other names	Bolero, Bolero 8EC, Bencarb, Saturn, Saturno, B 3015, IMC 3950, Siacarb, Tamariz
Empirical formula	C_{12}-H_{16}-Cl-N-O-S
Wiswesser line notation	GR D1SVN2&2 (HSDB, 1998)
Thiobencarb structure	

Identification numbers

Chemical Abstracts Service (CAS) Registry Number	28249-77-6
U.S. EPA Office of Pesticide Programs Chemical Code	108401
Hazardous Substances Data Bank (HSDB) Number	6846
Beilstein Reference Number	BRN 1968440
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)® Number	EZ7260000

Physical and Chemical Properties

Important physical and chemical properties of thiobencarb are given in Table 2. Thiobencarb (technical) is only slightly soluble in water but readily soluble in most organic solvents. When heated to decomposition, thiobencarb (technical) emits very toxic fumes of hydrogen chloride, nitrogen oxides, and sulfur oxides (HCl, NO_X and SO_X) (Sax, 1984).

Table 2. Physical and Chemical Properties of Thiobencarb.

Property	Value	References
Molecular weight	257.8 g/mol	WSSA, 1983
Color/Form	pale yellow or brownish liquid	ibid.
Corrosivity	relatively non-corrosive	ibid.
Density/Specific Gravity	1.145-1.180 at 20°C	ibid.
Melting point	3.3°C	Worthing *et al.*, 1987
Boiling point	126-129°C	Wiley and Sons, 1980
Vapor pressure	2.2×10^{-5} mm Hg (20°C)	U.S. EPA RED, 1997
Specific gravity	1.145-1.18	Saishin, 1989
Solubility in water @ 20°C	30 mg/L	Meister, 1998
Solubility in organic solvents @ 20°C (e.g., xylene, alcohols and acetone)	readily soluble	WSSA, 1983
Henry's Law constant	2.67×10^{-7} atm m^3/mole	Wauchope, 1991

Organoleptic Properties

Thiobencarb was associated with a taste problem in the drinking water in the City of Sacramento. Increases in complaints of bitter-tasting water were correlated with thiobencarb concentration in the Sacramento River. The bitter taste was believed to be caused by thiobencarb sulfoxide, which is a major oxidized product of thiobencarb generated during chlorination. The increase in consumer complaints always occurred when thiobencarb was detected at or above 1 ppb in the Sacramento River in May and June as a result of its discharges from thiobencarb-treated rice fields (DHS, 1987). There is no information on taste threshold for thiobencarb and its chlorination products. In order to protect the public welfare an SMCL of 1 ppb was established for thiobencarb. This SMCL is intended to prevent off-taste of drinking water from the Sacramento and American Rivers. The concentration of 1 ppb of thiobencarb and its degradation and oxidation products in drinking water does not represent a taste threshold. Neither it is a health-based value (such as a PHG). It was developed in response to the public complaints about the quality of drinking water delivered by public water systems.

Uses

Thiobencarb is also known by the name benthiocarb and the trade names Bolero and Saturn. It is a preemergent and early postemergent systemic herbicide used to control many broadleaf weeds, grasses, and sedge in food crops such as rice (95 percent of the United States use), lettuce, celery, and endive (U.S. EPA RED Facts, 1997; Meister, 1998). The primary target weed is barnyard grass, Echinochloa crus-galli, the most serious pest in rice. The amount of thiobencarb used in California in 1997 was 894,287 pounds (Cal/EPA, 1997). Ninety-eight percent of this amount was applied on rice.

Mode of Action

Thiobencarb acts by inhibiting shoots of emerging seedlings.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Thiobencarb is released directly to the environment through its use and application as an agricultural herbicide.

Soil

Thiobencarb binds to soil organic matter and it is not readily leached into water (WSSA, 1989). Biodegradation is the major mechanism of breakdown in soil (WSSA, 1989) and it occurs more rapidly in soils that have been acclimated to its use (Moon and Kuwatsuka, 1984). Microbial breakdown plays a major role in thiobencarb degradation (WSSA, 1983) which occurs also more rapidly in non-sterile soil and sediment systems than in sterile systems (Schimmel *et al.*, 1983; Walker *et al.*, 1988; Chen *et al.*, 1976). On soil surfaces exposed to sunlight, thiobencarb may be photodegraded to a certain extent, depending mainly on type of soil and temperature (WSSA, 1989; Chen *et al.*, 1976).

The half-life of thiobencarb in soil under aerobic conditions has been reported to be two to three weeks and under anaerobic conditions six to eight months (WSSA, 1989). The U.S. Department of Agriculture (USDA) Pesticide Properties Database lists 21 days as a soil half-life for thiobencarb (Wauchope *et al.*, 1991). Tests performed in three Florida soils exhibited half-lives for thiobencarb of 12 to 33 days (Braverman *et al.*, 1990).

In soil studies, ^{14}C-thiobencarb was degraded to approximately 20 compounds detectable by thin layer chromatography (TLC). The identified chemicals included unchanged thiobencarb, desethyl thiobencarb, thiobencarb sulfoxide, 4-chlorobenzoic acid, 2-hydroxythiobencarb and 4-chlorobenzyl alcohol. Under oxidative conditions degradation of thiobencarb was rapid and $^{14}CO_2$ was released from ^{14}C ring-labeled parent compound. The degradation process was much slower under flooded conditions (Menzie, 1980). When incubated in two soils from rice paddies, thiobencarb underwent dechlorination (Moon and Kuwatsuka, 1984); dechlorination did not occur in autoclaved soils (Moon and Kuwatsuka, 1984).

Thiobencarb may undergo surface runoff, with subsequent transport to rivers and lakes, after being applied to rice paddy fields as an herbicide (Shiraishi *et al.*, 1988; Iizuka *et al.*, 1985). In one study, about 2 percent of the total thiobencarb application was removed from a field through surface runoff (Iizuka *et al.*, 1985).

Water

Thiobencarb is resistant to degradation by hydrolysis. As in soil, a major environmental fate process for thiobencarb in the aquatic ecosystem is biodegradation (Schimmel *et al.*, 1983). The degradation process is much faster in non-sterile water/sediment systems than in sterile systems (Schimmel *et al.*, 1983; Walker *et al.*, 1988). Degradation in natural water may occur abiotically through photooxidation (Draper, 1984). The most likely route of this process is indirect photolysis via hydroxyl radicals (Draper, 1984).

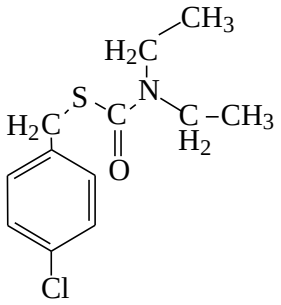
In a sterile pH 7 aqueous buffer solution, not pre-exposed to light (non-sensitized) at 25^{o}C, thiobencarb photodegraded with a calculated half-life of 190 days. More rapid photodegradation with a half-life of 12 days occurred in an acetone solution exposed to light. Thiobencarb did not degrade in the dark (non-sensitized control solution). The photoproducts identified in the non-sensitized and sensitized irradiated solutions were 4-chlorobenzoic acid, 4-chlorobenzaldehyde, 4-chlorobenzyl alcohol, and N, N-diethyl-4-(chlorobenzylthio) carbamate S-oxide (thiobencarb sulfoxide). In the non-sensitized solution, no photoproduct exceeded 3.9 percent of the applied thiobencarb. The major photoproducts in the sensitized solutions were 4-chlorobenzoic acid and 4-chlorobenzaldehyde, reaching maximum amounts of 56 and 29.4 percent of the initially applied amount of thiobencarb (Chen, 1988). In natural water, further degradation of 4-chlorobenzoic acid and 4-chlorobenzaldehyde varies greatly depending upon the content of organic particulate matter, the temperature and exposure to sunlight (HSDB, 1999a). It appears likely that thiobencarb, used as a pre-emergent and early post-emergent herbicide in rice fields in California, may spend a considerable period of time in relatively shallow, sunlit water where high percentages of its breakdown products 4-chlorobenzoic acid and 4-chlorobenzaldehyde might be generated.

U.S. EPA has evaluated persistence, mobility, and detection in ground water to determine whether to restrict the use of a chemical for ground water concerns. This evaluation resulted in the conclusion that ground water concerns do not warrant use restrictions of thiobencarb and that this chemical should not be a concern for ground water contamination nor human health because of its residues in drinking water derived from ground water (U.S. EPA, 1997). However, thiobencarb may contaminate surface waters as a result of releases of rice paddy water soon after field application, or from spray drift associated with aerial or ground spray application.

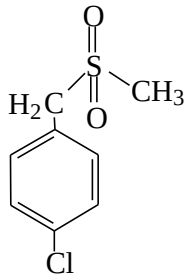
There is limited information on thiobencarb levels in ground water in the United States. According to the "Pesticides in Ground Water Database" (Hoheisel *et al.*, 1993), sampling for thiobencarb was done in 270 wells in California and 65 wells in Missouri. Only two detections of thiobencarb in ground water were reported in Missouri at very low levels of 0.2 to 0.3 ppb.

Food

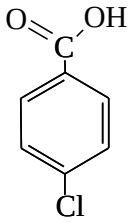
Thiobencarb and its chlorobenzyl and chlorophenyl moiety-containing metabolites (illustrated in Figure 1) have been detected as residues in food as a result of thiobencarb use in agriculture. In the United States, tolerances are currently established on the basis of combined residues of thiobencarb and its chlorobenzyl and chlorophenyl moiety-containing metabolites in or on agricultural commodities. They are listed under 40 CFR 180.401(a) and (b) as shown in Table 3.



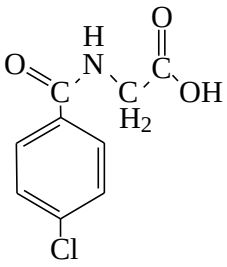
Thiobencarb



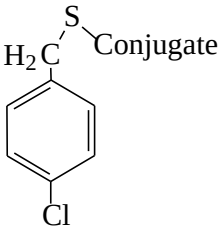
4-Chlorobenzymethylsulfone



4-Chlorobenzoic acid



N-(4-Chlorobenzoyl)glycine



4-Chlorobenzylthio conjugates

Figure 1. Thiobencarb and its Major Metabolites Containing the Chlorobenzyl and Chlorophenyl Moieties (adapted from U.S. EPA RED, 1997).

Probable Routes of Human Exposure

Human exposure to thiobencarb may occur as a result of occupational/agricultural activities (mixer/loader/applicator) or agricultural/gardening activities performed by non-trained persons such as homeowners, and by ingestion of food and drinking water with thiobencarb residues by the general population. The first two types of activities involve dermal contact and inhalation of dust.

Table 3. Tolerances for Residues of Thiobencarb in Foods.

Commodity	Concentration (ppm)
Cattle (fat, meat, meat byproducts)	0.2
Goat (fat, meat, meat byproducts)	0.2
Hog (fat, meat, meat byproducts)	0.2
Sheep (fat, meat, meat byproducts)	0.2
Poultry (fat, meat, meat byproducts)	0.2
Horse (fat, meat, meat byproducts)	0.2
Eggs	0.2
Milk	0.05
Rice, grain	0.2
Rice, straw	1.0
Celery, lettuce, endive (escarole)	0.2

METABOLISM AND PHARMACOKINETICS

Plants

Plants absorb and translocate thiobencarb from the site of its application. ^{14}C-Benzyl methylene labeled thiobencarb was taken up through the roots and translocated into the whole plants by rice, barnyard grass, wild amaranth, smartweed, and lambsquarters plants (Menzie, 1978). Translocation occurred also from one leaf into other leaves. When applied to seeds, thiobencarb was rapidly absorbed and accumulated mostly in the embryo.

In another experiment, roots of rice and barnyard millet were soaked in ^{14}C-thiobencarb solution for 48 hours. Degradation was rapid and most of the radioactivity in the plants was extractable with aqueous acetone. There was little difference observed in the metabolic pattern of both plants. The same metabolites were found in roots and foliage of both rice and barnyard millet. The metabolites were identified as desethyl thiobencarb, S-4-chlorobenzyl thiocarbamate, 4-chlorobenzoic acid, 2-hydroxythiobencarb, desethyl 2-hydroxythiobencarb, 4-chloro-2-hydroxybenzyl alcohol, and 4-chlorosalicylic acid. Hydrolysis of unextractable radioactivity with B-glucosidase and hydrogen chloride produced aglycons (Menzie, 1980).

Laboratory Animals

The disposition and metabolism of [phenyl-U-^{14}C]-thiobencarb was studied in male and female Sprague-Dawley rats at a single low oral dose (30 mg/kg), repeated low oral doses (30 mg/kg for

14 days), and a single high oral dose (300 mg/kg) (Jiang *et al.*, 1992). The rate of excretion indicated that thiobencarb was rapidly absorbed with no significant sex or dose group-related differences. The majority of radioactivity at all dose levels was eliminated in the urine and feces by 48 hours. At the high dose of 300 mg/kg the excretion was completed by 72 hours. There was no explanation provided for this delay. Repeated low oral dosing did not affect elimination of thiobencarb in either sex. There were also no significant sex- or dose-related differences in urinary or fecal excretion of thiobencarb-derived radioactivity.

Urinary excretion of [phenyl-U-^{14}C]-thiobencarb was a major route of elimination and there were no significant sex- or dose-related differences in amount of radioactivity excreted by this route. Among urinary and fecal metabolites of [phenyl-U-^{14}C]-thiobencarb, the glycine conjugate of 4-chlorohippuric acid was the major metabolite, which represented 74 to 81 percent of an administered dose in urine. Other detected metabolites included 4-chlorobenzyl methyl sulfoxide and sulfone, des-ethyl thiobencarb, and 4-chlorobenzoic acid, each accounting for less than 10 percent of an administered dose of thiobencarb. Neither the sex nor the single high or low repeated oral dose affected the urinary or fecal metabolite profile.

The metabolism of ^{14}C-thiobencarb was studied with white mice *in vivo* and *in vitro*. After oral administration, thiobencarb was rapidly translocated into organs. The majority of the labeled material was rapidly excreted in the urine. There was only slight excretion observed in feces and the least amount was expired. The major metabolites identified were 4-chlorohippuric acid, 4-chlorobenzoic acid, the glucuronide of 4-chlorobenzoic acid, and 4-chlorobenzyl alcohol. In *in vitro* studies the highest metabolic activity was exhibited in microsomal fraction of liver homogenates with NADP accelerating the degradation process. *In vitro* metabolites were identified as N-desethylthiobencarb, bis(4-chlorobenzyl) mono- and di-sulfides, and 4-chlorobenzoic acid (Menzie, 1978).

TOXICOLOGY

Toxicological Effects in Animals

The discussion presented below does not encompass studies with serious flaws in design or problems that developed during execution of the studies, such as inappropriate testing dose levels, excessive mortality, and cannibalization, or non-compliance with good laboratory practices (GLP) principles.

Acute Toxicity

Thiobencarb was studied in a variety of acute toxicity tests. Table 4 presents results of these tests in laboratory animals. Results of the acute tests presented above show that the technical thiobencarb can be assigned Toxicity Category III based on the oral (LD_{50} from 500 through 5000 mg/kg) and dermal (LD_{50} from 2000 through 20,000 mg/kg) exposures and toxicity category IV based on the results from inhalation (LC_{50} from 2.0 through 20 mg/liter) and dermal irritation tests (mild or slight irritation at 72 hours). Pesticide products meeting the criteria of Toxicity Category III and IV shall bear the signal word “Caution” on the label.

Subchronic Toxicity

Four groups of Sprague-Dawley rats received dermal application of Bolero 8EC (85.2 percent active ingredient) at doses of 0, 40, 160 or 500 mg/kg, five days per week during a 22-day period (Machado, 1993). Each group consisted of 72 animals (36/sex/dose) plus an extra six animals/sex/dose in the 0 and 500 mg/kg groups. The latter were held for two more weeks following the dosing period in order to observe a recovery process.

Table 4. Acute Toxicity Values for Technical Thiobencarb.

Animal	Test	Results (LD_{50})	References
Rat	Oral	920-1903 mg/kg	WSSA, 1983
Rat	Oral	1300 mg/kg	Worthing and Walker, 1987
Rat (M)	Oral	1033 mg/kg	Nishimura, 1985
		924-1155 mg/kg	ibid.
Rat (F)	Oral	1130 mg/kg 1033-1247 mg/kg	ibid.
Rat (M,F)	Dermal	> 2000 mg/kg	Nishimura, 1985
Rat	Percutaneous	2900 mg/kg	Worthing and Walker 1987
Rat	Inhalation	LC_{50} > 42.8 mg/L (1 hour)	Narcisse, 1976
Mouse	Oral	560 mg/kg	Worthing and Walker 1987
Rabbit	Dermal irritation	Slight irritation	U.S. EPA RED, 1997
Rabbit	Eye irritation	Slight irritation	U.S. EPA RED, 1997
Guinea pig	Dermal sensitization	Not a sensitizer	Silveira, 1982

A dose-related increase in the incidence of skin irritation was observed in treated compared to control rats of both sexes. In the mid- and high-dose groups, reduced food intake was accompanied by reduction in body weight gain. The reductions in the body weight gain persisted in high-dose males during the recovery period. A NOAEL of 40 mg/kg-day and a lowest-observed-adverse-effect-level (LOAEL) of 160 mg/kg-day were established for systemic toxicity based on decreases in body weight gain and food consumption in both sexes. No NOAEL was determined for dermal toxicity. The LOAEL was less than 40 mg/kg-day (the lowest dose tested) based on skin irritation.

Mutagenicity

Several tests are available on the mutagenic potential of thiobencarb (U.S. EPA RED, 1997; DPR, 1996). Pesticide testing for mutagenicity usually requires evaluation for gene mutation, chromosomal effects and DNA damage. A summary of genotoxicity testing of thiobencarb is presented in Table 5.

Table 5. Genotoxicity Testing of Thiobencarb.

Test System	Test organism	Concentration	Results	Reference
Ames test	*S. typhimurium*[a] TA100, TA98, TA1537 +/- S9	up to 50 µg/plate	Negative	U.S. EPA RED, 1997
Ames test	*S. typhimurium*[a] TA 98, TA100, TA1537+/- S9	0, 1, 10, 33, 50, 100 or 170 µg/plate	Negative	DPR, 1996
	TA100+/- S9	100 to 1,000 µg/plate	Negative	
Dominant Lethal	Mice	Single oral dose of 600 mg/kg and 300 mg/kg-day for five days	Negative	DPR, 1996
Clastogenicity	Human lymphocytes	0, 5, 10 and 20 µg/mL (- S9)	Negative	Boatman *et al.*, 1985
		0, 10, 20 and 40 µg/mL (+ S9)	Negative	
Micronucleus Test	Mice males	0, 270, 540 and 1,080 mg/kg	Positive	Boatman *et al.*, 1985
	Mice females	0, 405, 810 and 1,620 mg/kg	Positive	

The micronucleus assay was performed with thiobencarb technical (96 percent purity) in two experiments. In one, five male mice per group received a single oral dose of thiobencarb at 0, 270, 540 or 1,080 mg/kg. Female mice (five/group) received thiobencarb at doses of 0, 405, 810 or 1,620 mg/kg. A dose-related increase in micronuclei in polychromatic erythrocytes was observed, and was statistically significant in high dose males and in the two highest doses in females. In another experiment thiobencarb was administered by oral gavage in four daily repeated doses of 0 and 540 mg/kg to males and females (ten animals per group). Statistically significant increases in the incidence of micronuclei in the tested group were noted for both sexes.

As shown above, the majority of the currently available assays for evaluating genotoxic potential of thiobencarb were negative. No adverse effects were observed in the assays designed to determine potential for gene mutation (Ames tests) and in some tests for chromosomal aberration (dominant lethal assay and clastogenicity/cytogenetic analysis using human lymphocytes). However, the micronucleus assay is also designed to evaluate structural chromosomal aberration and thiobencarb produced a positive response in this regard. At present, we conclude that the existing data are not sufficient to determine thiobencarb's potential for DNA damage. Typical tests (to determine the latter effect) such as unscheduled DNA synthesis and sister chromatid exchange are not available for thiobencarb. Overall, thiobencarb shows weak genotoxic potential, at most.

Developmental and Reproductive Toxicity

Thiobencarb (97 percent purity) was administered by oral gavage to albino rats at 0, 5, 25 or 150 mg/kg-day on days 6 through 19 of gestation (Harris *et al.*, 1982; DPR, 1996). There were 27 to 30 rats per group. A NOAEL of 25 mg/kg-day was established for maternal toxicity. It was based on decreased body weight gain observed at 150 mg/kg-day level (LOAEL). This effect was not statistically significant. At the highest dose level of 150 mg/kg-day (LOAEL) there was also evidence of fetotoxicity demonstrated by decreased fetal weight, increased skeletal variation, delayed ossification, and an increase in the number of runts. Thus, a NOAEL for developmental toxicity was also at the level of 25 mg/kg-day.

In a developmental toxicity study in New Zealand white rabbits, technical thiobencarb (96.7 percent) was administered by gavage at the dose level of 0, 2, 20, 100 or 200 mg/kg-day from days 6 through 18 of gestation (Tauchi, 1970). At the highest dose level tested (200 mg/kg-day) maternal toxicity was manifested by a statistically significant increase in absolute and relative liver weights. A NOAEL identified in this study was therefore 100 mg/kg-day based on the increased liver weights. No developmental toxicity was observed at the dose levels tested. Consequently, the NOAEL for developmental effects was equal to or greater than 200 mg/kg-day and the LOAEL was greater than 200 mg/kg-day.

In another study with rabbits, thiobencarb (96 percent purity) was administered by oral gavage to 18 animals per group at dose levels of 0, 2, 20 or 100 mg/kg-day during days 7 through 29 of gestation (DPR, 1996). Maternal toxicity was manifested as a decreased weight gain in the mid and high dose groups (statistically significant in the high dose group) and increased incidence of premature delivery in the high dose group. The NOAEL for the maternal toxicity was therefore 2 mg/kg-day. The NOAEL for fetotoxicity was also 2 mg/kg-day. It was based on lower mean fetal weights in the mid and high dose groups which was not statistically significant.

In a two-generation reproduction study, thiobencarb (96.7 percent purity) was administered by oral gavage to Charles River Sprague-Dawley rats (25 animals/sex/group) in 0.5 percent sodium carboxy-methylcellulose solution at doses of 0, 2, 20 or 100 mg/kg-day, for 11 weeks pre-mating for F_0 parents and 13 weeks premating for F_1 generation (Hatakeyama, 1987; DPR, 1996). No effects on reproductive parameters were observed. The reproductive NOAEL was therefore equal to or greater than 100 mg/kg-day and the LOAEL was greater than 100 mg/kg-day. Systemic toxicity was observed at mid- and high-dose levels. It consisted of liver and kidney effects and a decreased weight gain at the high-dose level, especially in males. In the high-dose group, there were both absolute and relative increased liver and kidney weights. Liver effects were also manifested as hepatocyte single cell necrosis (both sexes of both generations, F_0 and F_1) and kidney effects involved atrophic tubules consisting of regenerated epithelium. For parental/systemic toxicity, the NOAEL was 2 mg/kg-day and the LOAEL was 20 mg/kg-day based on histopathological changes of the liver and kidney.

Based on the results of the above studies, the lowest NOAEL for both maternal (decreased weights and premature deliveries) and fetal toxicity (decreased fetal weight) was identified at 2 mg/kg-day in a rabbit developmental toxicity study of thiobencarb. These results are of less concern as indicators for developmental toxicity than they would be if the fetal effects occurred at levels of exposure lower than the maternal toxic effects. The parental NOAEL in the reproductive toxicity study was identified at the same level of 2 mg/kg-day as in the developmental toxicity study in rabbits.

Neurotoxicity

Acute Neurotoxicity

Bolero technical (thiobencarb 96.6 percent purity) was given in a single oral dose to male and female Sprague-Dawley rats, 12 or 16 animals (high dose level) per sex per group, at concentrations of 0 [0.7 percent carboxymethylcellulose sodium salt (high viscosity)/1 percent Tween 80], 100, 500 or 1,000 mg/kg (Lamb, 1994). One day before dosing, four hours post-dosing (time of peak effect), and on days 7 and 14 of the experiment, neurobehavioral evaluations were conducted consisting of a Functional Observational Battery (FOB) and motor activity. On day 15, rats were sacrificed and neuropathological examination was performed on control and high-dose animals (five/dose/sex).

All animals survived until terminal sacrifice with the exception of one female in the high-dose group, which died on day three of the study. Neither the mean body weight nor body weight gain of any of the treated animal groups was significantly different when compared with the control animal group. In animals at the high dose level there was an increased incidence of red deposits (the dried exudate of body fluids and blood) around the noses and mouths. In some females in this group gait abnormalities such as rocking, lurching and swaying were observed.

Neurobehavioral evaluation showed treatment-related changes using the FOB and motor activity findings at the mid- and high-dose levels. The effects were transient and observed only at the peak time of effect (four hours post-dosing).

Although not statistically significant, the incidences of changes in the FOB cannot be overlooked. When taken together, these results present a consistent treatment-related pattern of neurobehavioral signs. These signs consisted of gait abnormalities (lurching, swaying, and rocking), impaired mobility, and decreased sensory reactions (approach, touch, startle, tail pinch, and pupil responses). Mean body temperature was significantly decreased in all treated males and mid- and high-dose females. Hindlimb resistance was reduced in high-dose animals in both sexes. In the high-dose males, the startle response reached statistical significance at the time of peak effect, four hours post-dosing. In all mid- and high-dose animals total and ambulatory motor activity measured at the same time of peak effect showed significant treatment-related decreases. There were no treatment-related gross or neuropathological changes. Brain weights of the treated animals were comparable to those of control values. Both systemic and neurobehavioral effects observed in this study were identified at the same levels of exposures, 500 (LOAEL) and 1,000 mg/kg. The NOAEL established for systemic (based on increased red deposits and gait abnormalities) and acute neurobehavioral toxicity (based on gait abnormalities, decreased sensory responses, decreased body temperature, and decreased motor activity) is 100 mg/kg.

Subchronic neurotoxicity

In a subchronic neurotoxicity study (Lamb, 1993), Sprague-Dawley rats (10/sex/group) were administered thiobencarb (96.9 percent purity) by oral gavage at 0 [0.7 percent

carboxymethylcellulose sodium salt (high viscosity)/1 percent Tween 80], 2, 20 or 100 mg/kg-day for 13 weeks. All animals survived until terminal sacrifice. Body weight reduction was noted in males and females at 20 mg/kg-day (2 to 7 percent) and 100 mg/kg-day (2 to 10 percent) throughout the study period. However, food consumption was occasionally higher for 100 mg/kg-day female rats compared to the control animals.

Mean absolute and relative (to the terminal body weights) liver weights were statistically significantly increased in the two higher dose groups in comparison with control. Increases in mean absolute liver weights reached 12 percent for the 20 mg/kg-day male rats and 32 percent and 22 percent for the 100 mg/kg-day male and female rats, respectively. Relative liver weights were increased 15, 39, and 37 percent for the 20 mg/kg-day male rats and 100 mg/kg-day for male and female rats, respectively. At the highest dose level, mean absolute and relative (to the terminal body weights) kidney weights were also affected. Relative kidney weights were 27 and 24 percent higher than controls for male and female rats, respectively.

The functional observational battery open field observations exhibited an increased number in counts of "rearing" in female rats at weeks 3, 7, and 12. However, this increase was not statistically significant. Clinical signs were observed during the first four hours post-dosing. They included an increased incidence of a dried red deposit (the dried exudate of body fluids and blood) around the noses of all treated animals and dried tan or red exudate around the mouths of mid- and high-dose animals.

Histomorphological examination revealed mild changes in the sciatic, tibial and peroneal nerves in the high-dose male rats and changes in the sciatic nerve in the high-dose female rats. Changes in the sciatic nerve included axonal degeneration observed in one male and one female. The female rat effects included swollen axons seen in one animal and digestion chambers (alterations resulting from Schwann cell interaction in response to axonal degeneration) in another. Effects in tibial nerves consisted of axonal degeneration in one male rat and digestion chambers in two male rats. Digestion chambers were noted in peroneal nerves in two male rats

The study described above revealed signs of systemic toxicity and some indications of neurotoxic effects. A systemic NOAEL established in the study was <2 mg/kg-day (increased incidence of red exudate around nose at 2, 20 and 100 mg/kg-day). A LOAEL of 20 mg/kg-day was based on increased clinical signs (including red exudate around nose), decreased body weights and increased liver and kidney weights. The neurotoxicity NOAEL identified in this study was 20 mg/kg-day based on increased axonal degeneration and/or digestion chambers in sciatic, tibial, and peroneal nerves of high dose males compared with control animals.

There are some differences in the evaluation of the subject study by U.S. EPA (U.S. EPA RED, 1997) and DPR (1996). U.S. EPA (U.S. EPA RED, 1997) identified the systemic NOAEL as 2 and not <2 mg/kg-day because the increased incidence of dried red exudate around the noses of all treated animals including those in 2 mg/kg-day dose level was transient. This effect was noted only within the first four hours post-dosing. According to U.S. EPA, the NOAEL for neurotoxicity was greater than 100 mg/kg-day (HDT) and a LOAEL was not established (U.S. EPA RED, 1997). U.S. EPA did not address the histomorphological changes found in sciatic, tibial and peroneal nerves in high dose animals.

We conclude that a systemic NOAEL of <2 mg/kg-day and a neurotoxicity NOAEL of 20 mg/kg-day, as identified by DPR, are appropriate. Both systemic and neurotoxic changes seem to be treatment-related and should not be disregarded. This especially applies to the neurotoxic effects identified in the subchronic toxicity study. Though different, neurotoxic effects were also shown in the acute neurotoxicity study (Lamb, 1994).

Chronic Toxicity

Rats

In a combined chronic toxicity and carcinogenicity study, Fisher 344 rats were administered thiobencarb (95.3 percent purity) in the diet at 0, 20, 100 or 500 ppm (corresponding to approximately 0, 1, 5 and 25 mg/kg-day) for 108 weeks with 60 rats/sex/group (oncogenicity portion) and for 104 weeks with 20 rats/sex/group (chronic toxicity portion) (Ashby *et al.*, 1984). Interim sacrifices of ten males and ten females were performed at 28, 52, 79 and 104 weeks. Systemic toxicity was observed at 5 mg/kg-day and higher as decreased body weight gain, food consumption and food efficiency. There was also an increase in blood urea nitrogen at 5 and 25 mg/kg-day in both male and female rats and increases in packed red blood cell counts, red blood cell volumes, and hemoglobin concentration. The decreased weight gain can be partially attributed to palatability problems. There was no evidence of carcinogenicity at the dose levels tested. A NOAEL identified in this study for chronic toxicity was 1 mg/kg-day. A LOAEL of 5 mg/kg-day was identified based on decreased body weight gain, food consumption, food efficiency, and increased blood urea nitrogen in male and female rats and hematological changes in male rats.

Dogs

Beagle dogs (six animals/sex/dose) received 0, 1, 8 or 64 mg/kg-day of thiobencarb technical (96.3 percent purity) in gelatin capsules for 52 weeks (Johnson, 1985). At the highest dose level tested (64 mg/kg-day) in both male and female dogs, there were decreases in body weight gain and increases in absolute and relative kidney and liver weights. Decreases in serum albumin and protein (a slight effect was noted in mid-dose male dogs), erythrocyte counts and hemoglobin levels and reductions in hematocrit, alanine, and cholesterol level were also reported. From this study, a NOAEL of 1 mg/kg-day was established based on plasma cholinesterase inhibition noted at 8 (LOAEL) and 64 mg/kg-day in both sexes. Red blood cell cholinesterase inhibition was observed at the highest dose only and there were no changes in cholinesterase activity in the brain.

Carcinogenicity

Thiobencarb technical (93.7 percent purity) was administered to $B_6C_3F_1$ mice in the diet at 0, 25, 100, 400 or 1,600 ppm (0, 3, 14, 56 and 235 mg/kg-day for males and 0, 5, 19, 75 and 302 mg/kg-day for females, respectively) for 121 weeks (Macrae, 1982). There were 72 mice/sex/group. At 14 mg/kg-day in male mice, 19 mg/kg-day in female mice and in the higher dose groups of both sexes, there were histopathological changes in the liver. These changes included an increased incidence of discolored, not well perfused livers. At the highest dose level, male and female mice also exhibited increased incidences of fatty vacuolization (moderate or marked mid-zonal). At this level, in male mice only, there was marked fine fatty vacuolization and increased relative heart and liver weights. At 14 mg/kg-day and above, male mice exhibited decreased absolute and relative kidney weights. Female mice at the highest dose level exhibited increased relative kidney weights. Gross examination revealed an increased incidence of discolored (pale looking) foci of the lungs in both sexes at the highest dose tested (235 mg/kg-day) and discolored, not well perfused livers in the highest dose males (abdominal swelling noted during external examination). In male mice at this level, there was also an increased incidence of focal epithelialization of the alveolar walls of the lungs, with macrophages. Female mice at the highest dose level exhibited reduced body weight gains.

This toxicological study did not provide evidence of carcinogenicity in either sex at the dose levels tested. The chronic toxicity NOAELs based on histopathological changes in the liver were established at 3 mg/kg-day for male and 5 mg/kg-day for female mice. The LOAEL for male mice is 14 mg/kg-day and for female mice is 19 mg/kg-day.

Toxicological Effects in Humans

There are no data currently available on human toxicity for thiobencarb.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Review of the currently available toxicological data on thiobencarb indicates that the dose-response assessment should be based on noncarcinogenic adverse effects. The most appropriate study currently available for this purpose is the two-year rat feeding study (Ashby *et al.*, 1984). This is the same study used previously for establishing the PMCL for thiobencarb (DHS, 1987). The NOAEL of 1 mg/kg-day from this study is the lowest NOAEL determined from all of the currently available long-term studies. An identical NOAEL of 1 mg/kg-day was also established using the one-year dog chronic study (Johnson, 1985). Both studies were previously described in detail in this document.

The NOAEL of 1 mg/kg-day identified in the rat study was based on decreased body weight gain, food consumption, food efficiency (decreased weight gain per unit of food consumed), increased blood urea nitrogen both in male and female rats, and hematological changes in male rats observed at 5 mg/kg-day (the LOAEL). In the dog study, the NOAEL was based on plasma cholinesterase inhibition noted at 8 mg/kg-day (the LOAEL) in both sexes.

The NOAEL of 1 mg/kg-day was selected as the most appropriate dose level for calculating the PHG for thiobencarb. This value is scientifically supported by two long-term toxicity studies conducted in two species.

Carcinogenic Effects

No evidence of carcinogenicity was provided in the two long-term chronic toxicity studies, including a combined chronic toxicity study in rats (Ashby *et al.*, 1984) and an oncogenicity study in mice (Macrae, 1982). In the rat study, the animals were administered thiobencarb at 0, 1, 5 or 25 mg/kg-day. In the mouse study, the administered dose levels were 0, 3, 14, 56 or 235 mg/kg-day (for males) and 0, 5, 19, 75 or 302 mg/kg-day (for females). An overall evaluation of the available database on thiobencarb indicates that thiobencarb is not likely to be carcinogenic to humans because of the absence of significant tumor increases in chronic rodent studies and the lack of supportive findings in mutagenicity tests which, except for the micronucleus assay, were all negative (see Table 5).

Thiobencarb was ranked by the U.S. EPA RfD/Peer Review Committee as a Group D chemical, that is, not classifiable as to human carcinogenicity (February 8, 1996) (U.S. EPA RED, 1997.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets, and other household uses resulting in potential dermal and inhalation exposures.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for chemicals in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL = no-observed-adverse-effect-level or lowest-observed-adverse-effect-level,

BW = adult body weight (a default of 70 kg for male or 60 kg for female),

RSC = drinking water relative source contribution (usually in the range of 20 percent to 80 percent),

UF = uncertainty factors (typical defaults of 10 to account for inter-species extrapolation, 10 for uncertainty from the subchronic nature of the principal study and 10 for potentially sensitive human subpopulations), and

L/day = an adult daily water consumption rate (default of 2 L/day).

Calculation of a public health-protective concentration (C, in mg/L) for thiobencarb in drinking water based on the noncarcinogenic endpoint is presented below:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times L/day}$$

$$= \frac{1.0\ mg/kg\text{-}day \times 70\ kg \times 0.2}{100 \times 2\ L/day}$$

$$= 0.07\ mg/L\ (70\ ppb)$$

where,

NOAEL	=	no-observed-adverse-effect-level, approximately 1.0 mg/kg-day,
BW	=	adult body weight of 70 kg,
RSC	=	relative source contribution of 0.2 (default value),
UF	=	uncertainty factor of 100 (10 to account for inter-species extrapolation and 10 for potentially sensitive human subpopulations), and
L/day	=	an adult daily water consumption rate of 2 L/day.

Based on this calculation, we developed a PHG of 0.07 mg/L (70 ppb) for thiobencarb and its chlorobenzyl and chlorophenyl moiety-containing degradation products in drinking water. This PHG is calculated based on a NOAEL of 1.0 mg/kg-day for noncarcinogenic effects. These effects were noted in a combined chronic toxicity and carcinogenicity study in rats (Ashby *et al.*, 1984) and included decreased body weight gain, decreased food consumption and food efficiency, increased blood urea nitrogen in both male and female rats and hematological changes in male rats. The PHG is identical to the current California MCL of 70 ppb for this compound. Thiobencarb is not currently regulated under the Safe Drinking Water Act (SDWA). Therefore, there is no federal MCL.

RISK CHARACTERIZATION

There are no human toxicity data available on thiobencarb. However, its animal toxicology database is adequate for calculating a PHG.

The primary sources of uncertainty in the development of the PHG for thiobencarb in drinking water are the general issues of uncertainty in any risk assessment, particularly inter- and intra-species extrapolation and the relative source contribution (RSC) for thiobencarb in drinking water versus other exposure sources. Other uncertainties worth mentioning are those related to the quality of the currently existing database. These, in general, would include the lack of human data and specifically data on the metabolism and mechanism of toxicity of thiobencarb in humans and animals.

The extrapolation from toxicity studies in which thiobencarb was administered in feed to estimate the dose-response relationship for a drinking water standard for humans is uncertain. The amount and types of breakdown products generated in drinking water sources may be significantly different from the breakdown products generated in the feed of rats or dogs used in toxicity studies. Therefore, it is possible that the types and risks of chronic toxicity in humans exposed to these breakdown products are different from the type of chronic toxicity exhibited in the rat and dog toxicity studies in which the parent compound is administered. It is not likely to be feasible to administer thiobencarb in drinking water because of its limited solubility (see Table 2, page 3). This issue is of concern because of the high percentage of thiobencarb breakdown products generated in water under some conditions. In addition to this uncertainty, the usual uncertainty in inter-species extrapolation introduced by differing metabolism of the parent compound in rats and dogs relative to humans is present.

Further, little is known about endocrine disrupting effects of thiobencarb and whether there are certain groups more sensitive to this chemical than are average adults. Specifically, the existing database for thiobencarb does not indicate a potential for increased toxicological sensitivity for children.

Another uncertainty concerns a more complex issue relevant to aggregate health risk from exposures to chemicals that may have common toxicity endpoints with thiobencarb. At present, there are not enough data to determine whether thiobencarb and any other chemicals have a common mechanism of toxicity and would require a cumulative risk assessment. Thiobencarb is structurally related to thiocarbamate pesticides, but does not appear to produce toxic metabolites characteristic for other members of this group.

In developing the PHG for thiobencarb, we followed current U.S. EPA drinking water risk assessment methodology, including recommended default values for uncertainty factors, body weight, water consumption rate and RSC. The use of a value of 2 L/day for drinking water consumption reflects our interpretation that thiobencarb in water would not provide significant additional dermal and inhalation exposures in household uses such as showering. We used a standard default value of 20 percent for RSC assuming the remaining 80 percent of exposure comes from sources other than drinking water, mainly thiobencarb residues in food. Our judgment that the PHG should be derived from noncarcinogenic effects of thiobencarb is consistent with its classification as a "Group D" carcinogen by U.S. EPA.

The PHG of 70 ppb is considered adequate to protect sensitive subpopulations, including infants and children, from adverse health effects of thiobencarb in drinking water.

OTHER REGULATORY STANDARDS

Thiobencarb is not currently regulated under the Safe Drinking Water Act (SDWA). U.S. EPA has not established an MCL, which is the maximum permissible level of a contaminant in water delivered to any user of a public system, for thiobencarb.

The current California MCL of 70 μg/L (70 ppb) established for thiobencarb in 1987 was based on the same rat combined chronic toxicity/carcinogenicity study (Ashby *et al.*, 1984). We still consider this study and the identified NOAEL to be appropriate for calculating the PHG.

California also has a secondary maximum contaminant level (SMCL) of 1 ppb established for thiobencarb based on organoleptic properties. Both standards are part of California's drinking water regulations, and are enforceable.

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